REMARKS

Favorable consideration and allowance are respectfully requested for currently pending claims 1-28 in view of the following remarks.

The rejection of claims 27-28 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, is respectfully traversed.

The Office Action contends that the experimentation required to practice the claimed invention would be undue. However, given the highly advanced education and great skills of the persons who are of ordinary skill in the art (see page 4 of the Office Action), the experimentation would not be undue. The art of formulating pharmaceuticals is advanced and well developed. Based on the knowledge of the skilled artisan and the teachings provided in the specification, practicing the claimed invention is not an unpredictable venture.

The appropriate legal standard for enablement was stated by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (Fed. Cir. 1990):

> A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation. It is not fatal if some experimentation is needed. 15 USPQ 2d at 1329.

The U.S. Court of Customs and Patent Appeals has stated that "The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367 , 369 (CCPA 1971). The court also added that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go

to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 169 USPQ 367 , 370 (CCPA 1971). The present record includes no statement or other explanation as to why the truth of the accuracy of statements in the disclosure should be doubted. The law does not require a separate showing of functionality for each and every embodiment encompassed by a claim. Further, a specification need not provide an absolute guarantee of success to satisfy the enablement requirement. Rather, all that is required is a reasonable expectation of success.

Still further, Applicants are not required to provide a specific example of everything within the scope of their claims to establish enablement. *In re Anderson*, 176 USPQ 331 (CCPA 1973). Indeed, there is no *per se* requirement that an application provide any working examples, even in an unpredictable art. *Ex parte Wheeler*, 65 USPQ2d 1664 (BPAI 2002). Rather, the Court of Customs and Patent Appeals held that an application that specifically discloses a large number of compounds and asserts that other similar compounds may be made and used in the same fashion is adequate unless there is reason to suspect that the assertion is inadequate. *In re Barr*, 170 USPQ 330 (CCPA 1971).

According to claim 27, tramadol and diclofenac are released in amounts of more than 70 % and more than 60 % by weight, respectively, within 16 hours. Claim 28 limits the time period for this release to 8 hours.

The specification provides examples 1-4 which exhibit the following release profile at 8 hours.

Example	Release fraction of Tramadol in % by weight*	Release fraction of Diclofenac in % by weight*
1	79	71
2	89	78
3	98	72
4	98	99

* see the tables on pages 11, 13, 15 and 16 of the specification and Figures 1-4.

These examples demonstrate to the skilled artisan just how to achieve release profiles commensurate with that recited in claims 27 and 28. Any experimentation required to achieve the claimed release profile with other formulations would not amount to undue experimentation, but instead would merely be routine experimentation in the art of pharmaceutical formulation. Indeed, the highly skilled artisan in the art of formulating pharmaceuticals would have no difficulty in adjusting the release parameters of a given formulation so as to achieve the requirements of these claims.

Still further, as indicated in the MPEP at § 2164.08: "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." See, e.g., *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In the present instance, the scope of the claims is commensurate with the description provided in the specification. The examples provided in the specification represent preferred embodiments which demonstrate the operability of invention to achieve the parameters required by the claims. The skilled artisan has training and experience necessary to tailor pharmaceutical formulations. Based on this training and experience, the skilled artisan could readily practice the full scope of the invention as claimed, without undue experimentation.

Because the skilled artisan is highly skilled and has advanced education and experience and would be able to make and use the claimed invention in its full scope and because the patent laws do not limit the scope of allowable claims to the particular examples in the specification the present claims are adequately supported by the specification and the claims are fully enabled. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

The rejection of claims as obvious over Voss et al, US 4,690,927 and On, US 6,319,514 or Voss et al. and Raffa, EP 546,676 or the combination of Voss et al., Raffa or On, and Oshlack et al., US 6,077,533 are all respectfully traversed.

The present invention relates to the discovery that tramadol (hydrochloride) and diclofenac (sodium) form a sparingly soluble compound.

That is, when formulated together, these ingredients form a compound with a relatively low solubility. This low solubility is undesirable where there is a need to ensure that the active ingredients are released from the formulation within a short time following administration. By providing these active ingredients in separate subunits no such sparingly soluble compound is formed and the active ingredients may be release more quickly than if the active ingredients were simply mixed together.

Thus, providing the active ingredients in separate subunits provides an unexpected and unforeseen beneficial effect, namely that the release of the active ingredients can proceed much faster than if the ingredients were mixed together during the formulation process. In particular, in certain embodiments the invention allows the skilled artisan to achieve a release rate of tramadol (hydrochloride) and diclofenac (sodium) from a common administration unit which matches the release rate from administration units having only tramadol (hydrochloride) or diclofenac (sodium) as the active ingredient, see, e.g. paragraph [0048] of the present application and Figures 1, 3 and 4.

There is nothing in any of the cited art which even hints at these unexpected benefits. For instance, Voss et al. is silent as to any unfavorable physical or chemical interaction between tramadol and codeine. Further, in all of the specific examples provided in Voss et al. the active agents are mixed together, see col. 3, lines 11-12, 41-45 and 55-56. Voss provides no indication that there might be an unfavorable interaction between to active substances when they are provided together.

Even comparing the formulation where a core of diclofenac is surrounded by a layer of codeine as described at col. 2, lines 49-52 the benefit of the presently claimed invention is not achieved, because there is no chemical interaction whether between diclofenac and codeine, whether they are mixed together or provided in different layers. Thus, comparing the prior art to the claimed invention, in the prior art, the unexpected and unforeseen benefit of the presently claimed invention is not achieved.

The On reference is offered in the Office Action as teaching that tramadol may be substituted for codeine. There is no indication that such a substitution would result in a formulation with a delayed release profile. Indeed, the reality of the chemical interaction between tramadol and diclofenac shows that in fact, tramadal cannot simply be substituted for codeine. The formation of the sparing soluble compound of tramadol (hydrochloride) and diclofenac (sodium) indeed shows that there can be no simple substitution between the various anagesics.

As can be seen from Figure 2, if tramadol and diclofenac are embedded together in a conventional matrix tablet, the release profile of both active substances is disadvantageous.

The Raffa reference relates to a composition comprising a tramadol material and an NSAID. Raffa does not explicitly disclose the presently claimed combination of tramadol or a pharmaceutically acceptable salt thereof with diclofenac or a pharmaceutically salt thereof. Moreover, Raffa provides no indication that there might be any problem arising from the direct combination of tramadol and diclofenac.

Oshlack discloses sustained release oral solid dosage forms of opioid analgesics provided as multiparticulate systems containing pharmaceutically acceptable inert beads which are powder layered with therapeutically active agents. Oshlack does not disclose the presently claimed combination of tramadol and diclofenac nor the problem arising from the direct combination of these two active substances.

Considering the disclosures of the cited art, there is nothing to teach or suggest that the unexpected benefits afforded by the presently claimed invention might be achieved. Moreover, it is not clear from the record what would drive the skilled artisan to selectively consider only portions of teachings of the various cited references so as to arrive at the claimed invention. Rather, the proposed combination of these references and the modifications of these references necessary to arrive at the claimed invention is based purely on hindsight, relying on the present claims as a roadmap.

As pointed out by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 SCt 1727, 82 USPQ2d 1385, 1396 (U.S. 2007):

> [R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". (Quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329 (Fed. Cir. 2006) with approval).

Although an explicit teaching, suggestion or motivation need not be found in the cited references, to properly reject for obviousness, it is nevertheless necessary for the Examiner to articulate a convincing rationale as to what would lead a person skilled in the art to depart from the teachings of the prior art and strike out in the new direction claimed by applicants as their invention. In the present instance, the Office Action offers no persuasive rationale to explain why the skilled artisan would select a particular short sentence from Voss relating to a layered formulation and then disregard the remaining portion of the description and all of the examples teaching mixtures of active ingredients to and then try to combine On, Raffa or Oshlack. If anything, the skilled artisan would be inclined to disregard the teachings of the layered formulation since it would not simultaneously release the two active ingredients. Instead, in a lyered formulation as is described by Voss, first the outer layer is released, and hten only after the outer layer has been released, does the active ingredient in the inner core release.

Still further, when Raffa considers diclofenac or a pharmaceutically acceptable salt thereof as a possible active ingredient, it does so only in an extensive list of NSAIDs (see Raffa, page 3, line 50 to page 4, line 15). Raffa fails to describe any potential solubility or chemical interaction problem associated with the combination of tramadol and diclofenac. As indicated previously, Oshlack does not describe an oral dosage form where two active ingredients are provided, much less a dosage form where two active ingredients are provided in separate subunits. Instead, Oshlack describes formulations with the *same* active ingredient provided in different forms.

As stated previously, if one of skill in the art were, for some reason, to ignore Oshlack's description of single active ingredient dosage forms and try to combine tramadol with an NSAID in a dosage form as described in Oshlack, given Raffa's description of synergies between tramadol and NSAID's the person of skill in the art would be inclined to provide a combination of tramadol and NSAID together and spray this combination onto a single batch of beads. Thus, not only is there is nothing to cause one of skill in the art to go to the trouble of providing the tramadol and NSAID apart in separate subunits, as is required of the present claims, but instead, the art actually teaches away from such a formulation, so as to achieve the synergies Raffa describes.

As a result, it follows that a proper, case of obviousness has not been made out. Moreover, even if a showing of obviousness is believed to have been presented, it is overcome by the unexpected beneficial results achieved in accordance with the invention of the present claims. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No. 029310.50777CP).

Respectfully submitted,

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